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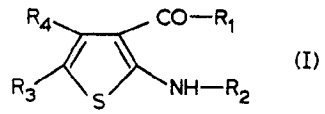
(54) 2-AMINO-3-CARBOXY-THIOPHENE DERIVATIVES

(71) We, BEECHAM GROUP LIMITED, a British Company of Beecham House, Great West Road, Brentford, Middlesex, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to derivatives of 2 - amino - 3 - carboxythiophene, to a process for their manufacture and to pharmaceutical compositions containing them which are useful in the treatment of inflammatory conditions such as arthritis.

The present invention provides compounds of the general formula (I):



(I)

wherein R_1 is NHR_5 or OR_5 where R_5 is a hydrogen atom or a lower alkyl group; R_2 is a hydrogen atom or a CO . R_6 group where R_6 is a lower alkyl group; one of the groups R_3 or R_4 is a substituted phenyl group and the other group R_3 or R_4 is a hydrogen atom or a lower alkyl or optionally substituted phenyl group; and salts thereof if COR_1 is an acid group.

When used herein, the term "lower alkyl" means an alkyl group of 1—6 carbon atoms. When used herein, the term "substituted phenyl" means the phenyl group substituted by a halogen atom or methyl, trifluoromethyl or methoxy group.

Preferably R_2 is a hydrogen atom.

Suitable groups R_5 include the hydrogen atom and the methyl, ethyl, n-propyl, isopropyl, butyl, pentyl and hexyl groups.

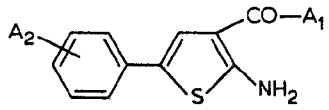
Preferred groups R_5 include the hydrogen atom and the methyl and ethyl groups.

Suitable groups R_6 include the methyl, ethyl and propyl groups.

The preferred groups R_6 are the methyl and ethyl groups.

Preferred groups R_4 include the hydrogen atom and the methyl, ethyl and phenyl groups, the hydrogen atom being particularly preferred.

One particular suitable sub-group of compounds within formula (I) are those of general formula (II):



(II)

wherein A_1 is a group of the formula OA_3 or NHA_3, where A_3 is a hydrogen atom or a lower alkyl group; and A_2 is a halogen atom or a methyl, trifluoromethyl or methoxy group.

Most suitably A_2 is a fluorine, chlorine or bromine atom or a trifluoromethyl group.

Preferably A_2 is a 4-fluorine atom.

Most suitably A_1 is an amino, methylamino, methoxy or ethoxy group.

Preferably A_1 is an amino group.

When the compound of the formula (I) is a carboxylic acid it may be in the form of an alkali metal salt, alkaline earth metal salt, ammonium or substituted ammonium salt or other conventional salt. Preferred salts include the sodium and potassium salts.

The compounds of formula (I) wherein R_2 is a hydrogen atom may be prepared by the reaction of sulphur and compounds of the general formulae (III) and (IV):

$$R_4\ CO\ .\ CH_2\ .\ R_3 \qquad \text{(III)}$$

$$NC—CH_2—CO—R_1 \qquad \text{(IV)}$$

wherein R_1, R_3 and R_4 are as defined in relation to formula (I). The compounds wherein R_1 is OH are more suitably prepared by the hydrolysis of a corresponding amide or ester.

This condensation reaction is similar to that described by K. Gewald, E. Schinke and H. Boetteher in *Chem. Ber., 99,* 94—100 (1966).

Normally the reaction is carried out in an

organic solvent such as dimethylformamide or similar inert solvent at non-extreme temperatures. Generally, the reaction temperatures are ambient or slightly elevated, for example, 15—100°C, preferably 30—80°C.

The condensation reaction is normally carried out in the presence of a base, such as diethylamine, morpholine or triethylamine.

Compounds of the formula (I) wherein R_2 is a COR_6 group may be prepared from the corresponding amino compound by conventional methods of acylation such as by reaction with an acid anhydride, or more suitably an acid halide, using for example, pyridine as a solvent.

The compounds of this invention possess useful anti-inflammatory activity. Accordingly, in a further aspect, the invention provides a pharmaceutical composition comprising a compound of the formula (I) as hereinbefore defined, together with a pharmaceutically acceptable carrier. Most suitably the compound of formula (I) included in the composition is one of formula (II) as hereinbefore defined.

The compositions of this invention may be in the form of conventional oral or parenteral unit dosage forms such as, for example, tablets, capsules, sachets, suppositories, and injectables. For convenience in administration oral forms such as tablets and capsules are preferred. Unit dose forms will normally contain from 6—600 mgs. of active compound, preferably 10—300 mgs, for example, 20—200 mgs.

The following examples illustrate the invention.

Example 1:

2 - Amino - 5 - (4 - fluorophenyl) - 3 - thiophene carboxamide

To a stirred mixture of cyanoacetamide (0.1 mole), sulphur (0.1 mole) and diethylformamide (20 ml) at 40—45° was added triethylamine (7.5 ml). The resulting dark brown solution was treated dropwise over 1½ hours, with 4 - fluorophenyl - acetaldehyde (0.1 mole) while the reaction mixture was maintained at 40—45°. After the solution had been stirred at room temperature for 16 hours, it was cooled (ice bath) and poured on to water (60 ml) at 5°C. The precipitate was collected by filtration, washed with water and dried. Recrystallisation from propanol yielded 2 - amino - 5 - (4 - fluorophenyl) - 3 - thiophenecarboxamide (40% by weight, m.p. 227—30°).

The following compounds were prepared in a similar manner to Example 1 and had the following melting points:

2 - Amino - 5 - (2 - fluorophenyl) - 3 - thiophene carboxamide, m.p. 170—1° (aqueous ethanol).

2 - Amino - 5 - (4 - methylphenyl) - 3 - thiophene carboxamide, m.p. 228—30° (ethanol).

2 - Amino - 5 - (4 - chlorophenyl) - 3 - thiophene carboxamide, m.p. 255—7° (ethanol).

2 - Amino - 5 - (3 - chlorophenyl) - 3 - thiophene carboxamide, m.p. 190—2° (ethanol).

Example 2:

2 - Acetamido - 5 - (4 - fluorophenyl) - 3 - thiophenecarboxamide.

A vigorously stirred mixture of 2 - amino - 5 - (4 - fluorophenyl) - 3 - thiophenecarboxamide (0.01 mole) and pyridine (20 ml) at 0° was treated dropwise with acetyl chloride (0.01 mole). The resulting solution was stirred a further 30 minutes at 0° and then poured on to cold water. The precipitate was collected by filtration, washed with water and dried. Recrystallisation from ethanol yielded 2 - acetamido - 5 - (4 - fluorophenyl) - 3 - thiophenecarboxamide (90% by weight, m.p. 230—3°).

Example 3.

2 - Amino - 5 - (4 - fluorophenyl) - 3 - thiophene N - methylcarboxamide

As example 1, except that N - methylcyanoacetamide replaced cyanoacetamide. The precipitate was recrystallised from aqueous ethanol to afford 2 - amino - 5 - (4 - fluorophenyl) - 3- thiophene N - methyl carboxamide in 40% by weight yield, m.p. 168° decomp).

Example 4:

Ethyl 2 - amino - 5 - (4 - fluorophenyl) - 3 - thiophene carboxylate

As example 1, except that ethyl cyanoacetate replaced cyanoacetamide. Recrystallisation of the crude product from hexane afforded ethyl 2 - amino - 5 - (4 - fluorophenyl) - 3 - thiophene carboxylate, m.p. 98—9°.

In a similar manner was prepared ethyl 2 - amino - 5 - (3 - chlorophenyl) - 3 - thiophene carboxylate, m.p. 110—11° hexane).

Example 5:

2 - Amino - 5 - (4 - fluorophenyl) - 3 - thiophene carboxylic acid.

A mixture of ethyl 2 - amino - 5 - (4 - fluorophenyl) - 3 - thiophene carboxylate (2g), sodium hydroxide (1g) and ethanol (20 ml) was refluxed for 5 hours, cooled and then concentrated. The solid residue was dissolved in water, filtered and acidified at 0°C. The light brown precipitate was collected by filtration to give pure 2 - amino - 5 - (4 - fluorophenyl) - 3 - thiophene carboxylic acid, m.p. 172—4°.

Example 6.

2 - Amino - 4 - (4 - chlorophenyl) - 3 - thiophene carboxamide.

A mixture of 4 - chloroacetophenone (100

g), cyanoacetamide (54.5 g), ammonium acetate (10 g), glacial acetic acid (32 g) and benzene (130 ml) was refluxed overnight with constant removal of water.

From the cooled solution was obtained pure (1 - (4 - chlorophenyl) - ethylidene cyanocetamide, m.p. 165—7°.

A mixture of 1 - (4 - chlorophenyl) - ethylidene cyanoacetamide (37.4 g), sulphur (5.43g), diethylamine (17 ml) and ethanol (70 ml) was stirred at 50—60° for 3 hours, cooled and added to water (200 ml). Recrystallisation of the crude product from benzene gave pure 2 - amino - 4 - (4 - chlorophenyl) - 3 - thiophene carboxamide, m.p. 159—60°.

In a similar manner was prepared 2 - amino - 4 - (4 - fluorophenyl) - 3 - thiophene carboxamide, m.p. 150—1° (ethyl acetate/hexane).

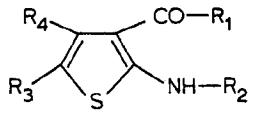
Example 7.

2 - Amino - 5 - (4 - fluorophenyl) - 4 - phenyl - 3 - thiophene carboxamide.

A mixture of 4 - fluorobenzyl phenyl ketone (50 g), morpholine (45 g) and benzene (100 ml) was refluxed overnight with molecular sieve, type 4A, to afford 2 - (4 - fluorophenyl) - 1 - phenyl - 1 - morpholinoethylene. The latter compound (0.2 mole), cyanoacetamide (0.2 mole), diethylamine (2 ml), sulphur (0.2 mole) and ethanol (100 ml) were stirred overnight at room temperature and then added to water. The crude product was recrystallised from ethanol and then from nitromethane to give pure 2 - amino - 5 - (4 - fluorophenyl) - 4 - phenyl - 3 - thiophene carboxamide, m.p. 205—7°.

WHAT WE CLAIM IS:—

1. A compound of the general formula (I):



(I)

wherein R_1 is NHR_5 or OR_5 where R_5 is a hydrogen atom or alkyl group of 1—6 carbon atoms; R_2 is a hydrogen atom or a $CO \cdot R_6$ group where R_6 is an alkyl group of 1—6 carbon atoms; one of R_3 or R_4 is a phenyl group substituted by a halogen atom or methyl, trifluoromethyl or methoxy group; and the other of R_3 and R_4 is a hydrogen atom or an alkyl group of 1—6 carbon atoms or a phenyl group optionally substituted by a halogen atom or methyl, trifluoromethyl or methoxy group; and salts thereof when COR_1 is an acid group.

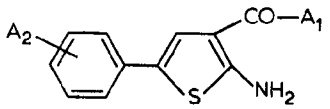
2. A compound as in Claim 1 wherein R_4 is a hydrogen atom or a methyl, ethyl or phenyl group.

3. A compound as in Claim 1 or 2 wherein R_5 is a hydrogen atom or a methyl or ethyl group.

4. A compound as in Claims 1—3 wherein R_2 is a hydrogen atom.

5. A compound as in Claims 1—4 wherein R_4 is a hydrogen atom.

6. A compound of the general formula (II):



(II)

wherein A_1 is OA_3 or NHA_3 where A_3 is a hydrogen atom or a lower alkyl group and A_2 is a halogen atom or a methyl, trifluoromethyl or methoxyl group.

7. A compound as in Claim 6 wherein A_2 is a fluorine, chlorine or bromine atom or a trifluoromethyl group.

8. A compound as in Claim 7 wherein A_2 is a 4-fluorine atom.

9. A compound as in Claims 6—8 wherein A_1 is a methylamino, methoxy or ethoxy group.

10. A compound as in Claims 6—8 wherein A_1 is an amino group.

11. 2 - Amino - 5 - (4 - fluorophenyl) - 3 - thiophene carboxamide.

12. A process for preparing a compound according to Claim 1 wherein R_2 is a hydrogen atom which comprises the reaction of sulphur and compounds of the general formulae (III) and (IV):

$$R_4 \cdot CO \cdot CH_2 \cdot R_3 \quad \text{(III)}$$

$$NC—CH_2 \cdot CO \cdot R_1 \quad \text{(IV)}$$

13. A process for preparing a compound according to Claim 1 wherein R_2 is $CO \cdot R_6$ which comprises acylating a compound according to Claim 1 wherein R_2 is a hydrogen.

14. A pharmaceutical composition which comprises a compound of the formula (I) as defined in Claim 1 together with a pharmaceutically acceptable carrier.

15. A compound according to Claim 1 as in any of the Examples herein.

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